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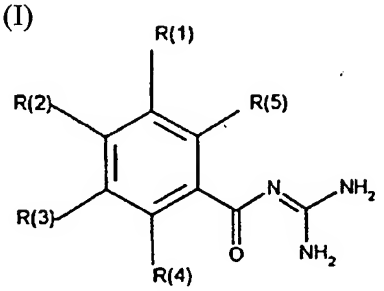
(54) **BENZOYLGUANIDINES BIS-ORTHO-SUBSTITUEES, PROCEDES DE PREPARATION, UTILISATION COMME MEDICAMENT OU PRODUIT DIAGNOSTIQUE, ET MEDICAMENT LES CONTENANT**

(54) **BIS-ORTHO-SUBSTITUTED BENZOYLGUANIDINES, PROCESSES FOR THEIR PREPARATION, THEIR USE AS A MEDICAMENT OR DIAGNOSTIC, AND MEDICAMENT COMPRISING THEM**

(I)



(57) Benzoylguanidines bis-ortho-substituées, procédés de préparation, utilisation comme médicament ou produit diagnostique, et médicament contenant ces composés. Les benzoylguanidines bis-ortho-substituées de formule I (voir formule I), où R(1) à R(5) ont les significations indiquées dans les revendications, conviennent comme produits pharmaceutiques antiarythmisants ayant un constituant cardioprotecteur pour la prévention et le traitement de l'infarctus et pour le traitement de l'angine de poitrine. Ils inhibent également, de manière préventive, les processus pathophysiologiques de la formation des lésions induites par l'ischémie, en particulier le déclenchement des arythmies cardiaques induites par l'ischémie.

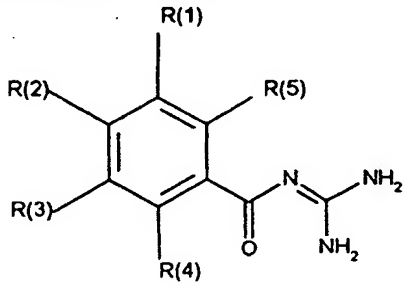
(57) Bis-ortho-substituted benzoylguanidines, processes for their preparation, their use as a medicament or diagnostic, and medicament containing them Bis-ortho-substituted benzoylguanidines of the formula I (see formula I) in which R(1) to R(5) have the meanings indicated in the claims, are suitable asantiarrhythmic pharmaceuticals having a cardioprotective component for infarct prophylaxis and infarct treatment, and for the treatment of angina pectoris. They also inhibit in a preventive manner the pathophysiological processes in the formation of is chemically induced damage, in particular in the elicitation of is chemically induced cardiac arrhythmias.

HOE 96/F 135

Abstract

Bis-ortho-substituted benzoylguanidines, processes for their preparation, their use as a medicament or diagnostic, and medicament containing them

Bis-ortho-substituted benzoylguanidines of the formula I



I

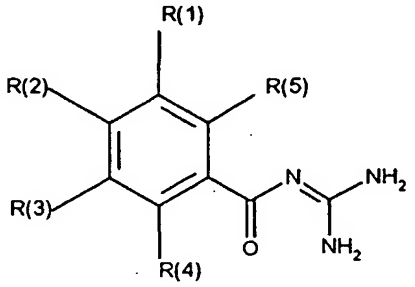
in which R(1) to R(5) have the meanings indicated in the claims, are suitable as antiarrhythmic pharmaceuticals having a cardioprotective component for infarct prophylaxis and infarct treatment, and for the treatment of angina pectoris. They also inhibit in a preventive manner the pathophysiological processes in the formation of ischemically induced damage, in particular in the elicitation of ischemically induced cardiac arrhythmias.

Hoechst Aktiengesellschaft HOE 96/F 135 Dr. v. F.

Description

Bis-ortho-substituted benzoylguanidines, processes for their preparation, their use as a medicament or diagnostic, and medicament comprising them

The invention relates to bis-ortho-substituted benzoylguanidines of the formula I



I

in which:

R(1), R(2) and R(3)

independently of one another are R(10)-SO_a- or R(14)R(15)N-SO_2-;

a is zero, 1 or 2,

R(10), R(14) and R(15)

independently of one another are alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, perfluoroalkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, alkenyl having 3, 4, 5 or 6 carbon atoms or -$C_{ab}H_{2ab}$-R(16);

ab is zero, 1, 2, 3 or 4;

R(16) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms, or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and NR(17)R(18);

R(17) and R(18)

independently of one another are hydrogen, CF_3 or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(14) and R(15)

together are 4 or 5 methylene groups, of which one CH_2 group can be replaced by oxygen, sulfur, NH, N-CH_3 or N-benzyl;

or

R(14) and R(15)

are hydrogen;

or

R(1), R(2) and R(3)

independently of one another are SR(21), -OR(22), -NR(23)R(24) or -CR(25)R(26)R(27);

R(21), R(22), R(23) and R(25)

independently of one another are -C_bH_{2b}-(C_1-C_9)-heteroaryl,

which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, CH_3, methoxy, hydroxyl, amino, methylamino and dimethylamino;

b is zero, 1 or 2;

R(24), R(26) and R(27)

independently of one another are hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are hydrogen, F, Cl, Br, I, CN, -$(Xa)_{dg}$-$C_{da}H_{2da+1}$, -$(Xb)_{dh}$-$(CH_2)_{db}$-$C_{de}F_{2de+1}$, alkenyl having 3, 4, 5, 6, 7 or 8 carbon atoms or -$C_{df}H_{2df}$R(30);

(Xa) is oxygen, sulfur or NR(33);

R(33) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

dg is zero or 1;

(Xb) is oxygen, sulfur or NR(34);

R(34) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

dh is zero or 1;

da is zero, 1, 2, 3, 4, 5, 6, 7 or 8;

db is zero, 1, 2, 3 or 4;

de is zero, 1, 2, 3, 4, 5, 6 or 7;

df is zero, 1, 2, 3 or 4;

R(30) is cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms, phenyl, biphenylyl or naphthyl,

the aromatic systems phenyl, biphenylyl or naphthyl being unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and NR(31)R(32);

R(31) and R(32)

are hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are NR(40)R(41) or $-(Xe)-(CH_2)_{eb}R(45)$;

R(40) and R(41)

independently of one another are hydrogen, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, perfluoroalkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms or $(CH_2)_e$-R(42);

e is zero, 1, 2, 3 or 4;

R(42) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and NR(43)R(44);

R(43) and R(44)

independently of one another are hydrogen, CF_3 or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(40) and R(41)

together are 4 or 5 methylene groups, of which one CH_2 group can be replaced by oxygen, sulfur, NH, N-CH_3 or N-benzyl;

(Xe) is oxygen, sulfur or NR(47);

R(47) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

eb is zero, 1, 2, 3 or 4;

R(45) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms, or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy, NR(50)R(51) and -(Xfa)-$(CH_2)_{ed}$-(Xfb)R(46);

Xfa is CH_2, oxygen, sulfur or NR(48);

Xfb is oxygen, sulfur or NR(49);

R(48), R(49), R(50) and R(51) independently of one another are hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

ed is 1, 2, 3 or 4;

R(46) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3) independently of one another are -CHR(52)R(53);

R(52) is -$(CH_2)_g$-$(CHOH)_h$-$(CH)_i$-$(CHOH)_k$-R(54) or -$(CH_2)_g$-O-$(CH_2$-$CH_2O)_h$-R(54);

R(54) is hydrogen or methyl;

g, h, i identically or differently are zero, 1, 2, 3 or 4;

k is 1, 2, 3 or 4;

R(53) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3) independently of one another are -C(OH)R(55)R(56);

R(55) and R(56) identically or differently are hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(55) and R(56) together are cycloalkyl having 3, 4, 5 or 6 carbon atoms;

or

R(55) is $-CH_2OH$;

and

R(4) and R(5)

independently of one another are alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, OH, F, Cl, Br, I, CN, $-O_n-(CH_2)_o-(CF_2)_p-CF_3$;

n is zero or 1;

o is zero, 1 or 2;

p is zero, 1 or 2;

and their pharmaceutically tolerable salts.

Preferred compounds of the formula I are those in which:

R(1), R(2) and R(3)

independently of one another are R(10)-SO_a-;

R(10) is alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, perfluoroalkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, alkenyl having 3, 4, 5 or 6 carbon atoms or $-C_{ab}H_{2ab}$-R(16);

ab is zero, 1, 2, 3 or 4;

R(16) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and NR(17)R(18);

R(17) and R(18)

independently of one another are hydrogen, CF_3 or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are -OR(22) or -CR(25)R(26)R(27);

R(22) and R(25)

independently of one another are $-C_bH_{2b}$-(C_1-C_9)-heteroaryl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, CH_3, methoxy,

hydroxyl, amino, methylamino and dimethylamino;

b is zero, 1 or 2;

R(26) and R(27)

independently of one another are hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are hydrogen, F, Cl, Br, I, CN, $-O_{dg}-C_{da}H_{2da+1}$, $-O_{dh}-(CH_2)_{db}-C_{de}F_{2de+1}$, alkenyl having 3, 4, 5 or 6 carbon atoms or $-C_{df}H_{2df}R(30)$;

dg is zero or 1;

dh is zero or 1;

da is zero, 1, 2, 3 or 4;

db is zero, 1, 2, 3 or 4;

de is zero, 1, 2, 3, 4, 5, 6 or 7;

df is zero, 1, 2, 3 or 4;

R(30) is cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms, phenyl, biphenylyl or naphthyl,

the aromatic systems phenyl, biphenylyl or naphthyl being unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl and methoxy;

or

R(1), R(2) and R(3)

independently of one another are $-O-(CH_2)_{eb}R(45)$;

eb is zero, 1 or 2;

R(45) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms or phenyl,

which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and $-(Xfa)-(CH_2)_{ed}-(Xfb)R(46)$;

Xfa is CH_2, oxygen, sulfur or NR(48);

Xfb is oxygen, sulfur or NR(49);

ed is 1 or 2;

R(46) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or

perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

R(48) and R(49)

independently of one another are hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are -CHR(52)R(53);

R(52) is $-(CH_2)_g-(CHOH)_h-(CH_2)_i-(CHOH)_k-R(54)$ or

$-(CH_2)_g-O-(CH_2-CH_2O)_h-R(54)$;

R(53) and R(54)

independently of one another are hydrogen or methyl;

g, h, i identically or differently are zero, 1 or 2;

k is 1 or 2;

or

R(1), R(2) and R(3)

independently of one another are -C(OH)R(55)R(56);

R(55) and R(56)

identically or differently are hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(55) and R(56)

together are cycloalkyl having 3, 4, 5 or 6 carbon atoms;

or

R(55) is $-CH_2OH$;

R(4) and R(5)

independently of one another are alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, OH, F, Cl, CN, $-O_n-(CF_2)_p-CF_3$;

n is zero or 1;

p is zero, 1 or 2;

and their pharmaceutically tolerable salts.

Particularly preferred compounds of the formula I are those in which:

R(1), R(2) and R(3)

independently of one another are R(10)-SO_2-;

R(10) is alkyl having 1, 2, 3 or 4 carbon atoms, perfluoroalkyl having 1, 2, 3 or 4 carbon atoms, alkenyl having 3, 4, 5 or 6 carbon atoms or -$C_{ab}H_{2ab}$-R(16);

R(16) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl and methoxy;

or

R(1), R(2) and R(3)

independently of one another are hydrogen, F, Cl, OH, CN, CF_3, alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 5 or 6 carbon atoms or alkoxy having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are -O-$(CH_2)_{eb}$R(45);

eb is zero or 1;

R(45) is cycloalkyl having 1, 2, 3 or 4 carbon atoms or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl and methoxy;

or

R(1), R(2) and R(3)

independently of one another are -$CH(CH_3)$-CH_2OH, -$C(OH)(CH_3)_2$ or -$C(OH)(CH_3)$-CH_2OH;

and

R(4) and R(5)

independently of one another are alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, OH, F, Cl, CN or -CF_3;

and their pharmaceutically tolerable salts.

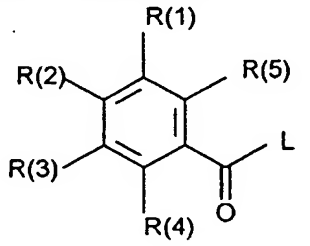
(C_1-C_9)-Heteroaryl is understood in particular as meaning radicals which are derived from phenyl or naphthyl, in which one or more CH groups are replaced by N and/or in which at least two adjacent CH groups are replaced by oxygen, sulfur or NH (with formation of a five-membered aromatic ring). In addition, one or both atoms of the fusion site of bicyclic radicals (as in indolizinyl) can be nitrogen atoms.

Heteroaryl counts in particular as furanyl, thienyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, indazolyl, quinolyl, isoquinolyl, phthalazinyl, quinoxalinyl, quinazolinyl, cinnolinyl.

If one of the substituents R(1) to R(5) contains one or more asymmetric centers, these can have either the S or the R configuration. The compounds can be present as optical isomers, as diastereomers, as racemates or as mixtures thereof.

The designated alkyl and perfluoroalkyl radicals can be straight-chain or branched.

The invention furthermore relates to a process for the preparation of the compound I, which comprises reacting a compound of the formula II



II

in which R(1) to R(5) have the meaning indicated and L is a leaving group which can be easily nucleophilically substituted, with guanidine.

The activated acid derivatives of the formula II in which L is an alkoxy group, preferably a methoxy group, a phenoxy group, phenylthio group, methylthio group or 2-pyridylthio group, a nitrogen heterocycle, preferably 1-imidazolyl, are advantageously obtained in a manner known per se from the underlying carbonyl chlorides (formula II, L = Cl), which for their part can in turn be prepared in a manner

known per se from the underlying carboxylic acids (formula II, L = OH), for example using thionyl chloride.

Beside the carbonyl chlorides of the formula II (L = Cl), further activated acid derivatives of the formula II can also be prepared in a manner known per se directly from the underlying benzoic acid derivatives (formula II, L = OH), such as the methyl esters of the formula II where L = OCH_3 by treating with gaseous HCl in methanol, the imidazolides of the formula II by treating with carbonyldiimidazole [L = 1-imidazolyl, Staab, Angew. Chem. Int. Ed. Engl. 1, 351 -367 (1962)], the mixed anhydrides II with Cl-$COOC_2H_5$ or tosyl chloride in the presence of triethylamine in an inert solvent; the activation of benzoic acids can also be carried out using dicyclohexylcarbodiimide (DCC) or using O-[(cyano(ethoxycarbonyl)-methylene)amino]-1,1,3,3-tetramethyl-uronium tetrafluoroborate ("TOTU")[Weiss and Krommer, Chemiker Zeitung 98, 817 (1974)]. A number of suitable methods for the preparation of activated carboxylic acid derivatives of the formula II are indicated with details of source literature in J. March, Advanced Organic Chemistry, Third Edition (John Wiley & Sons, 1985), p. 350.

The reaction of an activated carboxylic acid derivative of the formula II with guanidine is carried out in a manner known per se in a protic or aprotic polar but inert organic solvent. In the reaction of the methyl benzoates (II L = OMe) with guanidine, methanol, isopropanol or THF from 20°C up to the boiling temperature of these solvents have proven suitable here. In most reactions of compounds II with salt-free guanidine, the reaction was advantageously carried out in aprotic inert solvents such as THF, dimethoxyethane or dioxane. However, water can also be used in the reaction of II with guanidine, using a base such as, for example, NaOH as a solvent.

If L = Cl, the reaction is advantageously carried out with addition of an acid scavenger, e.g. in the form of excess guanidine for binding the hydrohalic acid.

Some of the underlying benzoic acid derivatives of the formula II are known and described in the literature. The unknown compounds of the formula II can be

prepared by methods known from the literature. The benzoic acids obtained are reacted according to one of the process variants described above to give compounds I according to the invention.

The introduction of some substituents into the benzene ring is carried out by methods known from the literature of palladium-mediated cross-coupling of aryl halides or aryl triflates using, for example, organostannanes, organoboronic acids or organoboranes or organocopper or -zinc compounds.

In general, benzoylguanidines I are weak bases and can bind acid with formation of salts. Possible acid addition salts are salts of all pharmacologically tolerable acids, for example halides, in particular hydrochlorides, lactates, sulfates, citrates, tartrates, acetates, phosphates, methanesulfonates and p-toluenesulfonates.

The compounds I are substituted acylguanidines.

EP-A 628 543 (HOE 93/F 154 - New Zealand Patent 260 681) discloses compounds which are also substituted in both ortho positions, but which in the 3-position always have an acyl or acylamino substituent, which is not present in the compounds according to the invention.

EP-A 690 048 (HOE 94/F 182 - New Zealand Patent 272 449) also describes compounds having substitution in both ortho positions, but of which one is always ortho-amino.

EP-A 704 431 (South Africa 95 07 161) describes compounds having an ortho substitution, but not with substitution in both ortho positions.

Compared to the known compounds, the compounds according to the invention are distinguished by an extremely high activity in the inhibition of Na^+/H^+ exchange.

Like the known compounds, they have no undesirable and disadvantageous salidiuretic properties, but very good antiarrhythmic properties, such as are

important, for example, for the treatment of illnesses which occur in the case of oxygen deficiency symptoms. On account of their pharmacological properties, the compounds are outstandingly suitable as antiarrhythmic pharmaceuticals having a cardioprotective component for infarct prophylaxis and infarct treatment, and for the treatment of angina pectoris, where they also inhibit or greatly decrease in a preventive manner the pathophysiological processes in the formation of ischemically induced damage, in particular in the elicitation of ischemically induced cardiac arrhythmias. Because of their protective effects against pathological hypoxic and ischemic situations, the compounds of the formula I according to the invention can be used as a result of inhibition of the cellular Na^+/H^+ exchange mechanism as pharmaceuticals for the treatment of all acute or chronic damage elicited by ischemia or illnesses induced primarily or secondarily by this means. This relates to their use as pharmaceuticals for surgical interventions, e.g. in organ transplantation, where the compounds can be used both for the protection of the organs in the donor before and during removal, for the protection of removed organs, for example during treatment with or storage thereof in physiological bath fluids, and also during transfer to the recipient's body. The compounds are also useful, protective pharmaceuticals when carrying out angioplastic surgical interventions, for example on the heart and on peripheral vessels. Corresponding to their protective action against ischemically induced damage, the compounds are also suitable as pharmaceuticals for the treatment of ischemias of the nervous system, in particular of the CNS, where they are suitable, for example, for the treatment of stroke or of cerebral edema. Moreover, the compounds of the formula I according to the invention are also suitable for the treatment of forms of shock, such as, for example, of allergic, cardiogenic, hypovolemic and of bacterial shock.

Moreover, the compounds of the formula I according to the invention are distinguished by potent inhibitory action on the proliferation of cells, for example fibroblast cell proliferation and the proliferation of vascular smooth muscle cells. The compounds of the formula I are therefore suitable as useful therapeutics for illnesses in which cell proliferation is a primary or secondary cause, and can therefore be used as antiatherosclerotics, agents against diabetic late complications, carcinomatous disorders, fibrotic disorders such as pulmonary

fibrosis, hepatic fibrosis or renal fibrosis, organ hypertrophies and hyperplasias, in particular in prostate hyperplasia or prostate hypertrophy.

The compounds according to the invention are effective inhibitors of the cellular sodium-proton antiporter (Na^+/H^+ exchanger), which is raised in numerous disorders (essential hypertension, atherosclerosis, diabetes, etc.) even in those cells which are easily accessible to measurements, such as, for example, in erythrocytes, platelets or leukocytes. The compounds according to the invention are therefore suitable as outstanding and simple scientific tools, for example in their use as diagnostics for the determination and differentiation of certain forms of hypertension, but also of atherosclerosis, of diabetes and of proliferative disorders, etc. Moreover, the compounds of the formula I are suitable for preventive therapy for the prevention of the genesis of high blood pressure, for example of essential hypertension.

It has additionally been found that compounds of the formula I have a favorable effect on serum lipoproteins. It is generally recognized that for the formation of arteriosclerotic vascular changes, in particular of coronary heart disease, excessively high blood lipid values, so-called hyperlipoproteinemias, are a significant risk factor. For the prophylaxis and the regression of atherosclerotic changes, the lowering of raised serum lipoproteins is therefore of extreme importance. Beside the reduction of the total serum cholesterol, the lowering of the proportion of specific atherogenic lipid fractions of this total cholesterol, in particular of the low density lipoproteins (LDL) and of the very low density lipoproteins (VLDL) is of particular importance, as these lipid fractions are an atherogenic risk factor. In contrast, the high density lipoproteins are ascribed a protective function against coronary heart disease. Accordingly, hypolipidemics should be able not only to lower the total cholesterol, but in particular the VLDL and LDL serum cholesterol fractions. It has now been found that compounds of the formula I have valuable therapeutically utilizable properties with respect to the effect on the serum lipid levels. Thus they significantly lower the raised serum concentrations of LDL and VLDL, as are to be observed, for example, as a result of increased dietetic uptake of a cholesterol- and lipid-rich diet or in the case of pathological metabolic changes, for example genetically related hyperlipidemias. They can therefore be used for the

prophylaxis and for the regression of atherosclerotic changes in that they eliminate a causal risk factor. These include not only the primary hyperlipidemias, but also certain secondary hyperlipidemias, such as occur, for example, in diabetes. Moreover, the compounds of the formula I lead to a marked reduction of the infarcts induced by metabolic anomalies and in particular to a significant decrease in the induced infarct size and its degree of severity. Furthermore, compounds of the formula I result in effective protection against damage due to metabolic anomalies of induced endothelial damage. With this protection of the vessels against the syndrome of endothelial dysfunction, compounds of the formula I are valuable medicaments for the prevention and for the treatment of coronary vascular spasms, of atherogenesis and of atherosclerosis, of left-ventricular hypertrophy and of dilated cardiomyopathy, and of thrombotic disorders.

The compounds mentioned are therefore advantageously used for the production of a medicament for the treatment of hypercholesterolemia; for the production of a medicament for the prevention of atherogenesis; for the production of a medicament for the prevention and treatment of atherosclerosis, for the production of a medicament for the prevention and treatment of illnesses which are induced by raised cholesterol levels, for the production of a medicament for the prevention and treatment of illnesses which are induced by endothelial dysfunction, for the production of a medicament for the prevention and treatment of atherosclerosis-induced hypertension, for the production of a medicament for the prevention and treatment of atherosclerosis-induced thromboses, for the production of a medicament for the prevention and treatment of hypercholesterolemia and endothelial dysfunction-induced ischemic damage and postischemic reperfusion damage, for the production of a medicament for the prevention and treatment of hypercholesterolemia and endothelial dysfunction-induced cardiac hypertrophies and cardiomyopathies, for the production of a medicament for the prevention and treatment of hypercholesterolemia and endothelial dysfunction-induced coronary vascular spasms and myocardial infarcts, for the production of a medicament for the treatment of the conditions mentioned in combinations with hypotensive substances, preferably with angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor antagonists, a combination of an NHE inhibitor of the formula I with a blood

lipid level-lowering active compound, preferably with an HMG-CoA-reductase inhibitor (e.g. lovastatin or pravastatin), the latter contributing a hypolipidemic action and thereby increasing the hypolipidemic properties of the NHE inhibitor of the formula I, proving to be a favorable combination with increased action and decreased use of active compound.

The administration of sodium-proton exchange inhibitors of the formula I as novel pharmaceuticals for lowering raised blood lipid levels is claimed, as well as the combination of sodium-proton exchange inhibitors with hypotensive and/or hypolipidemic pharmaceuticals.

Pharmaceuticals which contain a compound I can in this case be administered orally, parenterally, intravenously, rectally or by inhalation, the preferred administration being dependent on the particular clinical picture of the disorder. The compounds I can be used here on their own or together with pharmaceutical auxiliaries, in fact both in veterinary and in human medicine.

The person skilled in the art is familiar on the basis of his expert knowledge with the auxiliaries which are suitable for the desired pharmaceutical formulation. Beside solvents, gel-forming agents, suppository bases, tablet auxiliaries and other active compound excipients, antioxidants, dispersants, emulsifiers, antifoams, flavor corrigents, preservatives, solubilizers or colorants, for example, can be used.

For a form for oral administration, the active compounds are mixed with the additives suitable for this purpose, such as excipients, stabilizers or inert diluents, and brought by means of the customary methods into the suitable administration forms, such as tablets, coated tablets, hard gelatin capsules, aqueous, alcoholic or oily solutions. Inert excipients which can be used are, for example, gum arabic, magnesia, magnesium carbonate, potassium phosphate, lactose, glucose or starch, in particular corn starch. Preparation can take place here both as dry and as moist granules. Suitable oily excipients or solvents are, for example, vegetable or animal oils, such as sunflower oil or cod liver oil.

For subcutaneous or intravenous administration, the active compounds, if desired with the substances customary for this purpose such as solubilizers, emulsifiers or further auxiliaries, are brought into solution, suspension or emulsion. Possible solvents are, for example: water, physiological saline solution or alcohols, e.g. ethanol, propanol, glycerol, and in addition also sugar solutions such as glucose or mannitol solutions, or alternatively a mixture of the various solvents mentioned.

Pharmaceutical formulations suitable for administration in the form of aerosols or sprays are, for example, solutions, suspensions or emulsions of the active compound of the formula I in a pharmaceutically acceptable solvent, such as, in particular, ethanol or water, or a mixture of such solvents.

If required, the formulation can also contain still other pharmaceutical auxiliaries such as surfactants, emulsifiers and stabilizers, and also a propellant. Such a preparation customarily contains the active compound in a concentration of approximately 0.1 to 10, in particular of approximately 0.3 to 3, % by weight.

The dose of the active compound of the formula I to be administered and the frequency of administration depend on the potency and duration of action of the compounds used; additionally also on the nature and severity of the illness to be treated and on the sex, age, weight and individual responsiveness of the mammal to be treated.

On average, the daily dose of a compound of the formula I in the case of a patient of weight approximately 75 kg is at least 0.001 mg/kg, preferably 0.01 mg/kg, to at most 10 mg/kg, preferably 1 mg/kg, of body weight. In the case of acute episodes of the illness, for example immediately after suffering a cardiac infarct, even higher and especially more frequent doses may also be necessary, e.g. up to 4 individual doses per day. In particular in the case of i.v. administration, for example in the case of an infarct patient in the intensive care unit, up to 200 mg per day may be necessary.

List of abbreviations:

MeOH	methanol
DMF	N,N-dimethylformamide
RT	room temperature
EA	ethyl acetate (EtOAc)
M.p.	melting point
THF	tetrahydrofuran
eq.	equivalent

Experimental section

General procedure for the preparation of benzoyl guanidines (I)
Variant A: from benzoic acids (II, L=OH)

1.0 eq. of the benzoic acid derivative of the formula II is dissolved or suspended in anhydrous THF (5 ml/mmol) and then treated with 1.1 eq. of carbonyldiimidazole. After stirring for 2 hours at RT, 5.0 eq. of guanidine are introduced into the reaction solution. After stirring overnight, the THF is distilled off under reduced pressure (rotary evaporator), the residue is treated with water and adjusted to pH 6 to 7 with 2 N HCl, and the corresponding benzoylguanidine (formula I) is filtered off. The benzoylguanidines thus obtained can be converted into the corresponding salts by treating with aqueous, methanolic or ethereal hydrochloric acid or other pharmacologically tolerable acids.

General procedure for the preparation of benzoylguanidines (I)
Variant B: from alkyl benzoates (II, L = O-alkyl)

1.0 eq. of the alkyl benzoate of the formula II and 5.0 eq. of guanidine (free base) are dissolved in isopropanol or suspended in THF and heated to boiling (typical reaction time 2 to 5 h) until conversion is complete (thin -layer checking). The solvent is distilled off under reduced pressure (rotary evaporator), taken up in EA and washed 3 x with $NaHCO_3$ solution. The organic phase is dried over Na_2SO_4 ,

the solvent is distilled off in vacuo and the residue is chromatographed on silica gel using a suitable eluent, e.g. EA/MeOH 5 : 1.
(For salt formation compare variant A)

Example 1: 2,6-Dichlorobenzoylguanidine hydrochloride
Colorless crystals,
m.p. > 300°C, M^++H= 269,
from 2,6-dichlorobenzoic acid according to variant A.

Example 2: 3-Chloro-2,6-dimethoxybenzoylguanidine hydrochloride
Colorless crystals,
m.p. 148°C,
from 3-chloro-2,6-dimethoxybenzoic acid according to variant A.

Example 3: 4-Hydroxy-2,3,5,6-tetrafluorobenzoylguanidine hydrochloride
Colorless solid,
m.p. 184°C,
from 4-hydroxy-2,3,5,6-tetrafluorobenzoic acid according to variant A.

Example 4: 2,6-Difluorobenzoylguanidine hydrochloride
Colorless crystals,
m.p. 208 -10°C,
from 2,6-difluorobenzoic acid according to variant A.

Example 5: 2-Fluoro-6-trifluoromethylbenzoylguanidine hydrochloride
Colorless solid,
m.p. 178 - 80°C,
from 2-fluoro-6-trifluoromethylbenzoic acid according to variant A.

Example 6: 3-Trifluoromethyl-2,6-dimethoxybenzoylguanidine hydrochloride
Colorless crystals,
m.p. 189°C,
from 3-bromo-2,6-dimethoxybenzoic acid by reaction with potassium trifluoroacetate

in the presence of copper(I) iodide in dimethylformamide and subsequent reaction according to variant A.

Pharmacological data:

Inhibition of the Na^+/H^+ exchanger of rabbit erythrocytes

White New Zealand rabbits (Ivanovas) received a standard diet containing 2% cholesterol for six weeks in order to activate Na^+/H^+ exchange and thus to be able to determine Na^+ influx into the erythrocytes via Na^+/H^+ exchange by flame photometry. The blood was taken from the auricular arteries and rendered incoagulable by 25 IU of potassium heparin. A part of each sample was used for the duplicate determination of the hematocrit by centrifugation. Aliquots of 100 μl in each case were used to measure the Na^+ exchange content of the erythrocytes.

In order to determine the amiloride-sensitive sodium influx, 100 µl of each blood sample were incubated in 5 ml in each case of a hyperosmolar salt-sucrose medium (mmol/l: 140 NaCl, 3 KCl, 150 sucrose, 0.1 ouabain, 20 tris-hydroxymethylaminomethane) at pH 7.4 and 37°C. The erythrocytes were then washed three times with ice-cold $MgCl_2$-ouabain solution (mmol/l:112 $MgCl_2$, 0.1 ouabain) and hemolyzed in 2.0 ml of distilled water. The intracellular sodium content was determined by flame photometry.

The net Na^+ influx was calculated from the difference between sodium starting values and the sodium content of the erythrocytes after incubation. The amiloride-inhibitable sodium influx resulted from the difference between the sodium content of the erythrocytes after incubation with and without amiloride 3×10^{-4} mol/l. The same procedure was also used in the case of the compounds according to the invention.

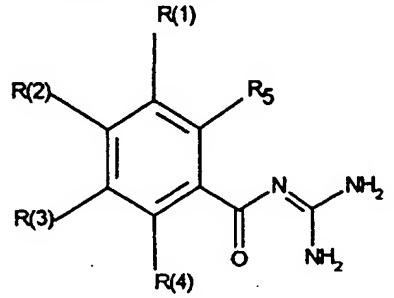
Results

Inhibition of the Na^+/H^+ exchanger:

Example	IC_{50} (µmol/l)
1	10
2	8.5
3	0.3
4	>10
5	10
6	>10

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A bis-ortho-substituted benzoylguanidine of the formula I



in which:

R(1), R(2) and R(3)

independently of one another are R(10)-SO_a- or R(14)R(15)N-SO_2-;

a is zero, 1 or 2,

R(10), R(14) and R(15)

independently of one another are alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, perfluoroalkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, alkenyl having 3, 4, 5 or 6 carbon atoms or -$C_{ab}H_{2ab}$-R(16);

ab is zero, 1, 2, 3 or 4;

R(16) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms, or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and NR(17)R(18);

R(17) and R(18)

independently of one another are hydrogen, CF_3 or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(14) and R(15)

together are 4 or 5 methylene groups, of which one CH_2 group can be replaced by oxygen, sulfur, NH, N-CH_3 or N-benzyl;

or

R(14) and R(15)

are hydrogen;

or

R(1), R(2) and R(3)

independently of one another are SR(21), -OR(22), -NR(23)R(24) or -CR(25)R(26)R(27);

R(21), R(22), R(23) and R(25)

independently of one another are $-C_bH_{2b}-(C_1-C_9)$-heteroaryl,

which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, CH_3, methoxy, hydroxyl, amino, methylamino and dimethylamino;

b is zero, 1 or 2;

R(24), R(26) and R(27)

independently of one another are hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are hydrogen, F, Cl, Br, I, CN, $-(Xa)_{dg}-C_{da}H_{2da+1}$, $-(Xb)_{dh}-(CH_2)_{db}-C_{de}F_{2de+1}$, alkenyl having 3, 4, 5, 6, 7 or 8 carbon atoms or $-C_{df}H_{2df}R(30)$;

(Xa) is oxygen, sulfur or NR(33);

R(33) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

dg is zero or 1;

(Xb) is oxygen, sulfur or NR(34);

R(34) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

dh is zero or 1;

da is zero, 1, 2, 3, 4, 5, 6, 7 or 8;

db is zero, 1, 2, 3 or 4;

de is zero, 1, 2, 3, 4, 5, 6 or 7;

df is zero, 1, 2, 3 or 4;

R(30) is cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms, phenyl, biphenylyl or naphthyl,

the aromatic systems phenyl, biphenylyl or naphthyl being unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and NR(31)R(32);

R(31) and R(32)

are hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are NR(40)R(41) or -(Xe)-$(CH_2)_{eb}$R(45);

R(40) and R(41)

independently of one another are hydrogen, alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, perfluoroalkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms or $(CH_2)_e$-R(42);

e is zero, 1, 2, 3 or 4;

R(42) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms or phenyl,

which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and NR(43)R(44);

R(43) and R(44)

independently of one another are hydrogen, CF_3 or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(40) and R(41)

together are 4 or 5 methylene groups, of which one CH_2 group can be replaced by oxygen, sulfur, NH, N-CH_3 or N-benzyl;

(Xe) is oxygen, sulfur or NR(47);

R(47) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

eb is zero, 1, 2, 3 or 4;

R(45) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms, or phenyl,

which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy, NR(50)R(51) and -(Xfa)-$(CH_2)_{ed}$-(Xfb)R(46);

Xfa is CH_2, oxygen, sulfur or NR(48);

Xfb is oxygen, sulfur or NR(49);

R(48), R(49), R(50) and R(51)

independently of one another are hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

ed is 1, 2, 3 or 4;

R(46) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are -CHR(52)R(53);

R(52) is -$(CH_2)_g$-$(CHOH)_h$-$(CH)_i$-$(CHOH)_k$-R(54) or -$(CH_2)_g$-O-$(CH_2$-$CH_2O)_h$-R(54);

R(54) is hydrogen or methyl;

g, h, i

identically or differently are zero, 1, 2, 3 or 4;

k is 1, 2, 3 or 4;

R(53) is hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are -C(OH)R(55)R(56);

R(55) and R(56)

identically or differently are hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(55) and R(56)

together are cycloalkyl having 3, 4, 5 or 6 carbon atoms;

or

R(55) is -CH_2OH;

and

R(4) and R(5)

independently of one another are alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, OH, F, Cl, Br, I, CN, $-O_n-(CH_2)_o-(CF_2)_p-CF_3$;

n is zero or 1;

o is zero, 1 or 2;

p is zero, 1 or 2;

and their pharmaceutically tolerable salts.

2. A compound of the formula I as claimed in claim 1, in which:

R(1), R(2) and R(3)

independently of one another are R(10)-SO_a-;

R(10) is alkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, perfluoroalkyl having 1, 2, 3, 4, 5, 6, 7 or 8 carbon atoms, alkenyl having 3, 4, 5 or 6 carbon atoms or $-C_{ab}H_{2ab}$-R(16);

ab is zero, 1, 2, 3 or 4;

R(16) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and NR(17)R(18);

R(17) and R(18)

independently of one another are hydrogen, CF_3 or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are -OR(22) or -CR(25)R(26)R(27);

R(22) and R(25)

independently of one another are $-C_bH_{2b}-(C_1-C_9)$-heteroaryl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, CH_3, methoxy, hydroxyl, amino, methylamino and dimethylamino;

b is zero, 1 or 2;

R(26) and R(27)

independently of one another are hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are hydrogen, F, Cl, Br, I, CN, $-O_{dg}-C_{da}H_{2da+1}$, $-O_{dh}-(CH_2)_{db}-C_{de}F_{2de+1}$, alkenyl having 3, 4, 5 or 6 carbon atoms or $-C_{df}H_{2df}R(30)$;

dg is zero or 1;

dh is zero or 1;

da is zero, 1, 2, 3 or 4;

db is zero, 1, 2, 3 or 4;

de is zero, 1, 2, 3, 4, 5, 6 or 7;

df is zero, 1, 2, 3 or 4;

R(30) is cycloalkyl having 3, 4, 5, 6, 7 or 8 carbon atoms, phenyl, biphenylyl or naphthyl,

the aromatic systems phenyl, biphenylyl or naphthyl being unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl and methoxy;

or

R(1), R(2) and R(3)

independently of one another are $-O-(CH_2)_{eb}R(45)$;

eb is zero, 1 or 2;

R(45) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms or phenyl,

which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl, methoxy and $-(Xfa)-(CH_2)_{ed}-(Xfb)R(46)$;

Xfa is CH_2, oxygen, sulfur or NR(48);

Xfb is oxygen, sulfur or NR(49);

ed is 1 or 2;

R(46) is hydrogen, alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

R(48) and R(49)

independently of one another are hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms or perfluoroalkyl having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are -CHR(52)R(53);

R(52) is $-(CH_2)_g-(CHOH)_h-(CH_2)_i-(CHOH)_k-R(54)$ or

$-(CH_2)_g-O-(CH_2-CH_2O)_h-R(54)$;

R(53) and R(54)

independently of one another are hydrogen or methyl;

g, h, i identically or differently are zero, 1 or 2;

k is 1 or 2;

or

R(1), R(2) and R(3)

independently of one another are -C(OH)R(55)R(56);

R(55) and R(56)

identically or differently are hydrogen or alkyl having 1, 2, 3 or 4 carbon atoms;

or

R(55) and R(56)

together are cycloalkyl having 3, 4, 5 or 6 carbon atoms;

or

R(55) is $-CH_2OH$;

R(4) and R(5)

independently of one another are alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, OH, F, Cl, CN, $-O_n-(CF_2)_p-CF_3$;

n is zero or 1;

p is zero, 1 or 2.

3. A compound of the formula I as claimed in claim 1 or 2, in which:

R(1), R(2) and R(3)

independently of one another are R(10)-SO_2-;

R(10) is alkyl having 1, 2, 3 or 4 carbon atoms, perfluoroalkyl having 1, 2, 3

or 4 carbon atoms, alkenyl having 3, 4, 5 or 6 carbon atoms or $-C_{ab}H_{2ab}$-R(16);

R(16) is cycloalkyl having 3, 4, 5, 6 or 7 carbon atoms or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl and methoxy;

or

R(1), R(2) and R(3)

independently of one another are hydrogen, F, Cl, OH, CN, CF_3, alkyl having 1, 2, 3 or 4 carbon atoms, cycloalkyl having 5 or 6 carbon atoms or alkoxy having 1, 2, 3 or 4 carbon atoms;

or

R(1), R(2) and R(3)

independently of one another are $-O-(CH_2)_{eb}R(45)$;

eb is zero or 1;

R(45) is cycloalkyl having 1, 2, 3 or 4 carbon atoms or phenyl, which is unsubstituted or substituted by 1 - 3 substituents selected from the group consisting of F, Cl, CF_3, methyl and methoxy;

or

R(1), R(2) and R(3)

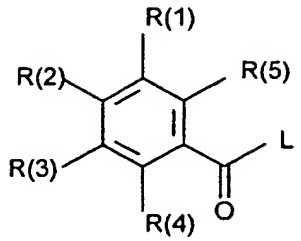
independently of one another are $-CH(CH_3)-CH_2OH$, $-C(OH)(CH_3)_2$ or $-C(OH)(CH_3)-CH_2OH$;

and

R(4) and R(5)

independently of one another are alkyl having 1, 2, 3 or 4 carbon atoms, alkoxy having 1, 2, 3 or 4 carbon atoms, OH, F, Cl, CN or $-CF_3$.

4. A process for the preparation of a compound of the formula I as claimed in claim 1, which comprises reacting a compound of the formula II



II

in which R(1) to R(5) have the meaning indicated and L is a leaving group which can be easily nucleophilically substituted,
with guanidine,
and optionally converting into a pharmacologically tolerable salt.

5. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of illnesses caused by ischemic conditions.

6. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of cardiac infarct.

7. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of angina pectoris.

8. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of ischemic conditions of the heart.

9. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of ischemic conditions of the peripheral and central nervous system and of stroke.

10. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of ischemic conditions of peripheral organs and members.

11. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment of states of shock.

12. The use of a compound I as claimed in claim 1 for the production of a medicament for use in surgical operations and organ transplantations.

13. The use of a compound I as claimed in claim 1 for the production of a medicament for the preservation and storage of transplants for surgical measures.

14. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment of illnesses in which cell proliferation is a primary or secondary cause, and thus their use for the production of an antiatherosclerotic, an agent against diabetic late complications, carcinomatous disorders, fibrotic disorders such as pulmonary fibrosis, hepatic fibrosis or renal fibrosis, and prostate hyperplasia.

15. The use of a compound I as claimed in claim 1 for the production of a medicament for the treatment or prophylaxis of disorders of lipid metabolism.

16. A pharmaceutical comprising an effective content of a compound of the formula I as claimed in claims 1 to 4.